REMARKS

Claims 23, 26, 28, 30-38, 40-43, and 61-70 are pending.

Claims 23 and 68 are amended herein.

Claims 71-78 are newly presented.

Support for the present amendment is found in the specification as originally filed. More specifically, support for "wherein exogenous nucleic acid is not incorporated into the target RNA species" in claim 23 is found at least at Drawing Sheet 5/15, Figure 5A; support for "phosphorothioate modification" in claim 68 is found at least at page 4, line 14; and support for claim 71-76 is found at least at page 18, line 8 through page 19, line 15; at page 21, lines 12-13; and at page 24, line 7 through page 26, line 1.

No new matter is introduced.

Applicants reserve the right to reintroduce cancelled subject matter, for example, in a later-filed continuing application.

Allowable Subject Matter

Applicants thank the Examiner for pointing out that "Seq ID No. 16 (recited in claim 70) appears free of the prior art searched and of record." Office Action at page 18, lines 10-12.

Disposition of Claim 43

At page 3, lines 4-5, the Office states that "Claim 43, as it pertains to diseases other than spinal muscular atrophy, is withdrawn from further consideration ..." However, Applicants note that claim 43 is rejected for reasons set forth in the instant Office Action. See, *e.g.*, Office Action at page 1, Summary, no. 6; and at pages 4, 6, and 14.

It is Applicants' understanding that claim 43, which reads on the elected species (*i.e.*, spinal muscular atrophy), is not withdrawn. If Applicants' understanding is incorrect, Applicants would appreciate clarification.

Information Disclosure Statement (IDS)

According to the Office, the IDS filed December 30, 2005 is non-compliant. Office Action at page 3, lines 9-19.

Applicants file herewith an IDS in compliance with the provisions of 37 CFR §1.97 and §1.98, and MPEP §609.

Claim Objection is rendered moot

Claim 68 is amended to recite "phosphorothioate," therefore, the objection to claim 68 is rendered moot. Office Action at page 18, lines 6-9.

Rejection of Claims under 35 U.S.C. §112, 1st paragraph (Written Description) is Traversed

The Office rejected claims 23, 26, 28, 30-38, 40-43, and 61-70 as allegedly failing to comply with the written description requirement. Office Action at pages 6-11. In view of the foregoing amendment and the following remarks, the rejection is traversed.

It appears that the Office has rejected the claims on the grounds that the application does not provide an adequate written description of the entire class of bifunctional oligonucleotides as claimed. Specifically, at pages 4-6 of the present Office Action, the Office takes the position that the specification does not describe a sufficient representative number of such oligonucleotides to describe the entire class, nor structural features to distinguish oligonucleotides that fall within the scope of the claims from those that do not. For example, according to the Office,

> The specification, claims and the art do not adequately describe the distinguishing features or attributes concisely shared by the members of the genus of compounds claimed, and which provide for the functions claimed ...

Office Action at page 4, last paragraph. Thus, the Office alleges that this amounts to an insufficient written description of these oligonucleotides.

Applicants point out that the two structural elements of the oligonucleotides as defined in the claims, namely (1) targeting/annealing sequences (*i.e.,* the first domain) and (2) binding motifs for RNA splicing factors (*i.e.,* the second domain or "tail"), are not only adequately described in the application but are well known in the art. For example, the targeting/annealing portion (*i.e.,* first domain) of the bifunctional oligonucleotide has to anneal to the target pre-mRNA by complementary base-pairing. And, the second domain has to be a sequence that, when added to the annealing portion, provides an additional positive contribution to RNA splicing at the desired site - for example, to enhance splicing, this second domain sequence will comprise a

splicing enhancer sequence, *i.e.* a sequence that normally stimulates splicing as an integral part of the pre-mRNA molecule.

With regard to the "annealing" portion (*i.e.,* first domain), any target RNA sequence provides a corresponding complementary sequence that is complementary to the RNA target species. The entire sequence of the human genome has been available for many years, along with the genome of an increasing number of other species. The person of skill in the art would readily be able to provide the sequence of a large number of suitable nucleic acid molecules for targeting to a specific splice site on a target RNA sequence.

Regarding the second domain or "tail," Applicants point out that the claimed invention is based on the inventors' surprising and unexpected finding that a splicing enhancer sequence part of an oligonucleotide (*i.e.,* "tail") can enhance splicing in *trans* when attached to the pre-mRNA *via* base-pairing of the annealing portion (*i.e.,* first domain) of the oligonucleotide. The inventors have tested this by using the tail sequences AGGAGGACGGAGGACGGAGGACA (based on the identification of a potent set of GGA repeats in the SK exon of TPM3 (Graham *et al.* (*i.e.,* Item 28 of the IDS filed herewith) and Watakabe *et al.* (*i.e.,* Item 29 of the IDS filed herewith)); AGGACGGAGGACGGAGGACA (truncated from the above sequence); AGGACCGCGGACCGCGGACA (which was first predicted to be an enhancer by functional SELEX; *e.g.,* Liu *et al.*, (*i.e.,* Item 30 of the IDS filed herewith)); and AGAAGAACGAAGAACGAGAACA (based on, *e.g.,* Tacke *et al.* (*i.e.,* Item 31 of the IDS filed herewith)) – each of which work well. Moreover, numerous other splicing enhancer sequences (*i.e.,* second domain) are described in the application, for example, the specification at page 12, lines 3-6 references Table 1 of Cartegni *et al.* (*i.e.,* Item 32 of the IDS filed herewith), which lists a number of RNA motifs that are recognized by human SR proteins. Also, page 13 of the present specification references a large number of motifs for binding splice-enhancers.

Thus, the application teaches a large number of suitable sequences. Many other suitable splicing enhancer sequences are known in the art and are described, for example, by references cited in the Watakabe *et al.* (*i.e.,* Item 29 of the IDS filed herewith); Cooper *et al.* (*i.e.,* Item 33 of the IDS filed herewith); Liu *et al.* (*i.e.,* Item 30 of the IDS filed herewith); Zhang *et al.* (*i.e.,* Item 34 of the IDS filed herewith); Zhang *et al.* (*i.e.,* Item 35 of the IDS filed herewith); Smith *et al.*

(*i.e.,* Item 36 of the IDS filed herewith); and Sanford *et al.* (*i.e.,* Item 37 of the IDS filed herewith).

For the foregoing reasons, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims under 35 U.S.C. §112, 1st paragraph(Enablement) is Traversed

The Office rejected claims 23, 26, 28, 30-38, 40-43, and 61-70 as allegedly lacking enablement. Office Action at pages 6-11. In view of the foregoing amendment and the following remarks, the rejection is traversed.

According to the Office:

> the specification, while being enabling for the in vitro increase in splicing efficiency by enhanced inclusion of exon 7 within SMN2 using particularly described 5'GGA and 5'GAA containing antisense oligonucleotides of SEQ ID NOs. 8 and 10, does not reasonably provide enablement for methods of recruiting RNA splicing factors, enhancing exonic incorporation, and recruiting any splicing factor to any target RNA species for treating any condition characterized by defective RNA splicing in an individual, comprising the administration of a representative number of species of the broad genus of compounds claimed.

Office Action at page 6, line 14 through page 7, line 2.

First, Applicants wish to point out that, in addition to the *in vitro* examples, the instant specification also discloses *in vivo* examples with cultures of fibroblasts derived from patients with spinal muscular atrophy (SMA). See, *e.g.,* Specification at page 59, line 16 through page 63, line 4; and at page 67, lines 2-9.

Nonetheless, the Office appears to take the position that the claims must be limited to the specific *in vitro* examples. However, the Office has not provided reasons to doubt the ability of a person skilled in the art to make and use the claimed invention without ***undue*** experimentation. Moreover, the Office's evidence of the degree of experimentation required merely consists of five journal articles that either lack relevancy to the claimed invention or that do not stand for the proposition asserted by the Office. In fact, even the Office's own position appears inconsistent with the Office's assertion in the same Office Action at page 17, lines 4-8 and last three lines:

> Furthermore, it would have required routine experimentation to design nucleic acid molecules targeting the mutation site and relying on the methods taught previously by Mitchell [(US 2003/0077754)] and Mitchell [(US 2004/0126774)].

> One of ordinary skill in the art would have had a reasonable expectation of success for correcting the exon skipping phenomenon associated with SMA ...
>
> One of ordinary skill in the art would also have been motivated to incorporate 2'-O-methyl and/or phosphorothioate internucleotide modifications into nucleic acid molecules for target cell delivery and uptake ...

But, Applicants point out that there are numerous instances of clinical trials and scientific papers that support enablement as it relates to the claimed invention. The Office must do more than simply provide isolated excerpts from references that do not fairly reflect the state of the art at the time the application was filed.

Clinical trials and Scientific Literature Negate the Office's Assertion

There are multiple instances including clinical trials and scientific literatures that negate the Office's assertion regarding alleged lack of enablement. In this regard, Applicants submit, by way of the IDS filed herewith, evidence that negates the alleged lack of enablement:

Item 38

Item 38 (dated November 1999) discusses phase I study of an antisense oligonucleotide to protein kinase C-α in patients with cancer. According to the authors of Item 38:

> Patients with incurable malignancies received ISIS 3521, a 20-length phosphorothioate oligodeoxynucleotide specific for PKC-α. Treatment was delivered over a period of 21 days by continuous i.v. infusion followed by a 7-day rest period.
>
> Between August 1996 and September 1997, 21 patients were treated in five patient cohorts.
>
> Evidence of tumor response lasting up to 11 months was observed in three of four patients with ovarian cancer.
>
> Evidence of antitumor activity provides the rationale for Phase II studies in ovarian cancer and other malignancies.

Item 39

Item 39 (dated May 14, 1997) reports the use of modified fragments of antisense nucleic acid to stop the production of a cancer cell protein. Item 39 reports (emphasis added):

> The researchers delivered the drug directly into the bloodstream, thereby distributing it throughout the body. "What's intriguing to me is that you can

actually get these bits of modified DNA into cancer cells by giving them intravenously," Sikic said.

Dr. Branimir Sikic, professor of medicine (oncology and clinical pharmacology) at Stanford University Medical Center, will present the results of the Phase I clinical trial on the morning of Monday, May 19, at the meeting of the American Society for Clinical Oncology in Denver.

One of the first patients to participate, a woman from Oregon with ovarian cancer, has experienced a remission, or tumor shrinkage, for more than eight months. As with the other patients in this study, her cancer had been resistant to previous chemotherapy. Two other patients with ovarian cancer have some indications of an anti-tumor effect, but Sikic cautioned that it is too early to be certain that these patients are having remissions.

Item 40

Item 40 (dated August 15, 1996) reports clinical trials of antisense compounds to target human cytomegalovirus (CMV). Item 40 reports:

Hybridon's first clinical drug candidate, GEM(R)91 for the treatment of HIV-I infection and AIDS, is currently in Phase Ib/II clinical trials. The antisense drug has been safely administered to more than 170 subjects at leading medical centers in the United States, France and the United Kingdom.

Hybridon plans to start clinical trials for intravitreal administration of GEM132 in December 1996 in the United States and Europe. The Company also plans to submit a second Investigational New Drug (IND) Application in early 1997 for the systemic formulation of GEM132 in the United States. Hybridon's first clinical drug candidate, GEM(R)91 for the treatment of HIV-I infection and AIDS, is currently in Phase Ib/II clinical trials. The antisense drug has been safely administered to more than 170 subjects at leading medical centers in the United States, France and the United Kingdom.

GEM132 is a "hybrid" molecule comprised of a strand of synthetic DNA with a protective cap of modified RNA at each end. This novel design of GEM132 is designed to protect the drug from degradation by natural enzymes in the body, thereby improving metabolic stability, which might result in less frequent dosing.

In tissue culture tests, GEM132 has demonstrated anti-viral activity with a potency about 1,000 times greater than ganciclovir, the leading therapy for HCMV. GEM132 has demonstrated significant anti-viral activity in vitro against human clinical isolates and isolates which have become resistant to ganciclovir and foscarnet, another drug currently being used to treat HCMV disease.

Item 41

Item 41 (dated June 2, 2000) reports Phase 1 clinical trial of an anti HIV-1 antisense gene therapy product, HGTV-43. Item 41 reports:

> These results show an unprecedented eight-month survival of the engineered cells in an HIV-infected individual among the group studied and the development of CD4+ cells expressing the HIV-1 antisense RNA within the cell. Such antisense genes have previously been shown to provide resistance to the virus.
>
> Our ultimate goal is to achieve for HIV-1 infected individuals a long-term, lifelong immune responsiveness in a disease characterized by progressive loss of this defensive mechanism. Based on the results thus far we believe we have made significant progress towards this goal," said Dean Engelhardt, Ph.D., a Senior Vice President of Enzo.

Additionally, in further support of enablement, Applicants also submit (by way of the IDS filed herewith) the following evidence:

Item 42 is a press release by AVI BioPharma highlighting the success of Dr. Francesco Muntoni's (one of the instant inventors) work. Item 42 reports that the first human tests in the UK for the use of RNA oligonucleotides to combat DMD by exon skipping technology have been very successful.

Item 43 (*i.e.,* Graham *et al.*) discusses the use of oligonucleotides to affect splicing and restore the production of dystrophin in a mouse model *in vivo* by administering the oligonucleotides to muscle cells (see page 1155, right column, "The effect of spliceomer P on restoration of dystrophin production *in vivo*").

Item 44 (*i.e.,* van Deutekom *et al.*) describes successful early-stage trials on four human patients aged 10-13 who were intramuscularly administered RNA oligonucleotides to correct the dystrophin reading fame by antisense-mediated exon skipping technology.

Item 45 (*i.e.,* Pennisi) provides a brief review of clinical trials and results of *in vivo* models using exon-skipping antisense technology for treating Duchenne Muscular Dystrophy.

Item 46 (*i.e.,* Wilton *et al.*) provide a review of exon skipping technology for the treatment of Duchenne Muscular Dystrophy. In the abstract, the authors state:

> A clinical trial has recently confirmed proof-of-principle that exclusion of Exon 51 from human dystrophin mRNAs, carrying frame-shifting deletions adjacent to this exon, results in dystrophin expression. No major side-effects after local administration of the antisense oligomer were reported. Additional trials are underway...

Item 47 (*i.e.,* Sussman *et al.*) describe the use of Monarsen, a synthetic 20-base antisense oligodeoxynucleotide that affects splicing of the acetylcholinesterase pre-mRNA, in a phase 1b study for the treatment of myasthenia gravis. The authors conclude that oral administration of Monarsen resulted in marked improvements in the severity of myasthenia gravis (page 289).

Item 48 (Bauman *et al.*) provides a review of the therapeutic potential of splice switching technology using synthetic oligonucleotides. Table 1 on page 2 lists nine conditions in which the technology has been validated by clinical trials, animal models, and *in vivo* cellular models.

Accordingly, at least in view of the foregoing evidence, Applicants assert that the claimed invention is enabled.

The Art, Specifically, Supports Enablement of the Claimed Invention

Moreover, a number of scientific publications *specifically* support the enablement of the claimed invention. For example, as evidence, Applicants submit (by way of the IDS filed herewith) Items 50-53, each of which specifically references the inventors' published work, namely, Skordis *et al.*, Bifunctional antisense oligonucleotides provide a trans-acting splicing enhancer that stimulates SMN2 gene expression in patient fibroblasts. PNAS, 100: 4114–4119 (2003) (*i.e.,* Item 49 of the IDS filed herewith).

For example, Item 50 (*i.e,* Meyer *et al.*) discusses "rescue of a severe mouse model for spinal muscular atrophy using U7 snRNA-mediated splicing modulation." Moreover, in the final paragraph of the Discussion section at page 1484, Item 51 (*i.e.,* Marquis *et al.,)* states that:

> In conclusion, the strategy based on bifunctional U7 snRNAs presented here is extremely promising for future preclinical and clinical work on SMA ... Additionally, we note that this strategy could be used to promote exon inclusion in other situations as well. In an even wider context U7 RNAs can be designed to carry additional binding sites for any conceivable RNA-binding proteins or other ligands thereby providing for a wide range of potential therapeutic and diagnostic applications.

Moreover, at page 330, right column, last paragraph, Item 52 (*i.e.*, Khoo *et al.*) states:

> Nevertheless, these two papers have shown a proof of concept with great promise. This will be an exciting avenue for targeted, therapeutic modification or alternative splicing, with wide applicability to other diseases caused by defective splicing.

And, according to Item 53 (*i.e.*, Gottlieb *et al.*) at page 3, right column, lines 5-7:

> In principle, the technique could provide the ability to correct RNA-splicing defects associated with any gene or disease.

Thus there are a number of papers that specifically support the enablement of the claimed invention. Not only has the presently claimed invention been demonstrated to work in animal models *in vivo*, but it was also considered in the art to provide a wide range of potential therapeutic and diagnostic applications.

References Cited by the Office Do Not Support The Office's Position

In support of its enablement rejection, the Office cites (1) S. Crooke, Ann. Rev. Med., Vol. 55, pages 61095, 2004, esp. pages 71072, 74, 81, 84-85 ("Crooke"); (2) Branch, Trends in Biochem. Sci., 23, 45-50, 1998 ("Branch"); (3) Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51 ("Peracchi"); (4) Chirila et al, Biomaterilas, Vol. 23, pages 321-342, 2002, especially pages 326-327 ("Chirila") ; and Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80 ("Agrawal"). However, Applicants' submit that the relied on references do not support the Office's position regarding the alleged lack of enablement.

Crooke

According to the Office, "Crooke also points out that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules." Office Action at page 7, lines 18-19.

However, none of the pages of Crooke referenced by the Office state that cell culture examples are generally not predictive of *in vivo* inhibition of target molecules, nor is such a statement reasonable from the disclosure of Crooke as a whole. Crooke is actually a highly positive article that describes progress in antisense technology, and provides details of a number of antisense-type drugs that have been successful in clinical trials or in *in vivo* experimentation (See, *e.g.*, Crooke at pages 74-77). Thus, not only does Crooke not support the examiner's contention of a lack of enablement, rather, the entire disclosure of Crooke appears to support Applicants' assertion that a person of ordinary skill in the art can carry out the methods of the present invention without undue experimentation.

Branch

The Office also cites Branch, Trends in Biochem. Sci., 23, 45-50, 1998 ("Branch") for the proposition that "the in vivo (whole organism) application of molecules is a highly unpredictable endeavor due to target accessibility and delivery issues." Office Action at page 7, lines 16-18.

However, Applicants point out that Branch is not relevant to the claimed invention at least because, according to Branch, "[o]nly antisense molecules and ribozymes designed to inhibit RNA target sequences are considered here." (See, *e.g.*, Branch at page 46, left column, lines 14-16). But the present invention is not directed to antisense molecules or ribozymes. Although Branch, citing reference 15 (*i.e.,* Sierakowska *et al.*, PNAS, 93:12840-12844, (1996) (*i.e.,* Item 54 of the IDS filed herewith)), states that "many of the same principles apply to other nucleic acid drugs ... such as those used to alter RNA splicing," Branch's reference 15 does not discuss any difficulty in using antisense to affect splicing. Branch at page 46, left column, lines 14-20. Indeed, Branch's reference 15 (*i.e.,* Item 54 (Sierakowska *et al.*)) successfully restored correct splicing in cells *in vivo*, and stated that the approach was clinically promising, and is of general applicability. Thus, Branch is not relevant to the present invention, much less supportive of the Office's contention of a lack of enablement.

Peracchi

The Office also cites Peracchi et al, Rev. Med. Virol., 14, pages 47-64, 2004, abstract on page 47 and text on page 51 ("Peracchi"). According to the Office,

> Peracchi cites stability and delivery obstacles that need to be overcome in achieving desired in vivo efficacy: "A crucial limit of ribozymes in particular, and of oligonucleotide-based drugs in general, lies in their intrinsically low ability to cross biological membranes, and therefore to enter cells where they are supposed to operate ... cellular uptake following systemic administration appears to require more sophisticated formulations ... the establishment of delivery systems that mediate efficient cellular uptake and sustained release ... remains one of the major hurdles in the field."

Office Action at page 7, line 22 through page 8, line 7.

At pages 51-52 of the Introduction, Peracchi mentions two main routes for administering ribozymes *in vivo*: a gene therapy type approach based on delivery from a vector, and exogenous delivery of ribozymes themselves. Peracchi acknowledges that its article is barely concerned with gene therapy based delivery, which is described in detail on pages 23-25 of the instant application - this is one enabling route to delivery of oligonucleotide-based drugs. Moreover, Peracchi, while acknowledging that "a crucial limit of ribozymes in particular, and of

oligonucleotide-based drugs in general, lies in their intrinsically low ability of cross biological membranes, and therefore to enter the cells where they are supposed to operate" (page 51, right column), proceeds to describe a number of solutions to this difficulty.

Chirila

The Office also cites Chirila et al, Biomaterilas, Vol. 23, pages 321-342, 2002, especially pages 326-327 ("Chirila") "for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells." Office Action at page 8, lines 8-15.

But, Applicants point out that Chirila discusses the use of polymers as carriers for delivery of oligodeoxynucleotides. According to Chirila, "some of the proposed carriers (cationic polymers, biodegradable polymers) showed promising results." Chirila at page 337, left column, lines 30-31. Thus, even if one considers that use of polymers is not an optimal method for delivery of some oligonucleotide-based drugs, nonetheless, this represents an enabling route of administration and delivery.

Agrawal

The Office also cites Agrawal et al, Molecular Med. Today, Vol. 6, pages 72-81, 2000, especially at pages 79-80 ("Agrawal") "for a general review of the important and inordinately difficult challenges of the delivery of therapeutic molecules to target cells." Office Action at page 8, lines 8-15.

Agrawal, which predates the filing date of the present application, does not support a lack of enablement rejection against therapeutic delivery of oligonucleotides as alleged by the Office. For example, Table 1 of Agrawal on page 74 lists 16 oligonucleotides in clinical trials using different routes of delivery. Moreover, Agrawal states that "a PS-oligonucleotide targeted to human cytomegalovirus (CMV) has been approved for the treatment of CMV-induced retinitis. Many other antisense oligonucleotides are at various stages of clinical development (Table 1)." Agrawal at page 72, right column, lines 5-11. Thus, Agrawal does not support the examiner's contention of a lack of enablement.

Accordingly, not only do the references cited by the Office fail to support the Office's position regarding the alleged lack of enablement, the evidence presented herein actually

supports Applicants' assertion that the specification would have enabled the claimed method for one skilled in the art at the time of filing.

For the foregoing reasons, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims under 35 U.S.C. §102(e) is Traversed or Rendered Moot

Mitchell et al (US 2003/0077754)

The Office rejected claims 23, 26, 28, 30-38, 40-42, and 61-65 as allegedly anticipated by Mitchell et al (US 2003/0077754). Office Action at pages 12-13. In view of the foregoing amendment and the following remarks, the rejection is traversed or rendered moot.

Although Applicants in no way acquiesce with respect to this rejection as applied to the previously pending claims, Applicants have amended claim 23 in an effort to further enhance the clarify of the nature of the invention intended to be claimed. In particular, the recitation "wherein exogenous nucleic acid is not incorporated into the target RNA species" is added to emphasize that the claimed method is distinguishable from Mitchell et al (US 2003/0077754), which discusses *trans-splicing* "in which a portion of the PTM [*i.e.,* exogenous nucleic acid] is spliced to the natural pre-mRNA ..." See, *e.g.*, Mitchell et al (US 2003/0077754) at page 2, paragraph [0013], lines 10-13.

Accordingly, Mitchell et al (US 2003/0077754) does not anticipate the claimed method, therefore, Applicants respectfully request that the rejection be withdrawn.

Mitchell et al (US 2004/0126774)

The Office rejected claims 23, 26, 28, 30-38, 40-42, 61-65, and 69 as allegedly anticipated by Mitchell et al (US 2004/0126774). Office Action at pages 12-13. In view of the foregoing amendment and the following remarks, the rejection is traversed or rendered moot.

Although Applicants in no way acquiesce with respect to this rejection as applied to the previously pending claims, Applicants have amended claim 23 in an effort to further enhance the clarify of the nature of the invention intended to be claimed. In particular, the recitation "wherein exogenous nucleic acid is not incorporated into the target RNA species" is added to emphasize that the claimed method is distinguishable from Mitchell et al (US 2004/0126774), which discusses *trans-splicing* "in which a portion of the PTM [*i.e.,* exogenous nucleic acid] is

spliced to the natural pre-mRNA ..." See, *e.g.*, Mitchell et al (US 2004/0126774) at page 2, paragraph [0013], lines 10-13.

Accordingly, Mitchell et al (US 2004/0126774) does not anticipate the claimed method, therefore, Applicants respectfully request that the rejection be withdrawn.

Rejection of Claims under 35 U.S.C. §103(a) is Traversed or Rendered Moot

The Office rejected claims 23, 26, 28, 30-38, 40-43, 61-69 as allegedly obvious over Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774) as applied to claims 23, 26, 28, 30-38, 40-42, 61-65, and 69, and further in view of Lim et al (J. Biol. Chem., Vol. 276, No. 48, pages 45476-45483, 2001), and Lorson et al (Proc. Natl. Acad. Sci., Vol. 96, pages 6307-6311, 1999), the combination further in view of Dunckley et al (Human Molec. Genetics, Vol. 5, No. 1, pages 1083-1090, 1995). Office Action at pages 14-18. In view of the foregoing amendment and the following remarks, the rejection is traversed or rendered moot.

Applicants restate the discussion above as it relates to Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774). The additional secondary references cited here, namely Lim *et al.*, Lorson *et al.*, and Dunckley *et al.*, are set forth as allegedly providing only various elements of further dependent claims. They are not set forth as curing the noted deficiencies of Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774) as discussed above. It is believed that none of the references cure the noted deficiencies of Mitchell et al (US 2003/0077754) and Mitchell et al (US 2004/0126774) as noted herein.

Accordingly, Applicants respectfully request that the rejection be withdrawn and that the claims be allowed.

Secondary Considerations

Even if, solely for the sake of argument, Applicants assume that a *prima facie* assertion of obviousness has been established, important secondary indicia of nonobviousness support patentability of the present invention.

Acclamations by Experts in the Field

With respect to acclamations by experts in the field as discussed below, Applicants point out Items 51-53 and 55 submitted by way of the IDS filed herewith. For example, with reference to the inventors' work, Item 55 at paragraph six reports (emphasis added):

> Paula Grabowski, Howard Hughes Medical Institute investigator at the University of Pittsburgh, cited a similar approach reported by L.A. Skordis and colleagues. The UK researchers designed oligonucleotides that were complementary to a portion of the exon missing in the SMN2 gene and that also contained a tail with sequences that enhance exon splicing. The designer molecule increased incorporation of the missing exon in patient fibroblasts. Grabowski called the work, "One of the most important advances this year in alternative splicing."

Moreover, the authors of Item 52 (*i.e.,* Khoo *et al.*) refer to the inventors' approach as an "exciting and unique approach" to compensate for SMN1 deficiency by upregulating the amount of full-length SMN2 transcripts (see, *e.g.*, Item 52 at page 329, left column, lines 9-12), and further state that:

> Nevertheless, these two papers have shown a proof of concept with great promise. This will be an exciting avenue for targeted, therapeutic modification or alternative splicing, with wide applicability to other diseases caused by defective splicing.

Similarly, the inventors' approach is also discussed by Item 53 (*i.e.*, Gottlieb *et al.*). In this regard, the authors of Item 53 state (at page 3, right column, lines 5-7):

> In principle, the technique could provide the ability to correct RNA-splicing defects associated with any gene or disease.

Further, Item 51 (Marquis *et al*), for example, states:

> The strategy based on bifunctional U7 snRNAs presented here is extremely promising for future preclinical and clinical work on SMA ... Additionally, we note that this strategy could be used to promote exon inclusion in other situations as well. In an even wider context U7 RNAs can be designed to carry additional binding sites for any conceivable RNA-binding proteins or other ligands thereby providing for a wide range of potential therapeutic and diagnostic applications.

Accordingly, the present invention has received industry acclamation as evidenced by at least the foregoing articles (*i.e.,* Items 51-53 and 55).

For at least the foregoing reasons, no combination of references relied on by the Office could have provided Applicants' invention as presently claimed. Accordingly, Applicants respectfully request that the rejections be withdrawn and that the claims be allowed.

CONCLUSION

Applicants believe these Amendments and Remarks place the claims in condition for allowance/issuance and such action is respectfully requested. If issues may be resolved through Examiner's Amendment, or clarified in any manner, a call to the undersigned attorney is respectfully requested.

Respectfully submitted,

Date: April 20, 2009

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